REMARKS

Claims 45, 48-49, 53-55, 57, 59, 69-76 are pending in the present application after entry of the present amendments. Claim 69 has been amended to more particularly point out and distinctly claim the present invention. Claims 43, 44, 46, 47, 50, 51, 52, 56, 58, 60-68 have been canceled without prejudice. Applicants reserve the rights to prosecute the canceled and amended subject matter in related applications. The amendments are supported by the originally filed specification and claims, *e.g.*, *see p.*1, *ll.* 5-7; *p.* 4, *ll.* 2-4, *ll.* 12-16; *p.*15, *ll.* 9-13; and *p.* 17, *ll.* 23-*p.* 18, *ll.* 4. Accordingly, the amendments are fully supported by the specification and do not introduce any new matter. Applicants submit herewith a copy of European patent EP 1 181 555 B1 with the granted claims, which is the corresponding European patent of the above-captioned application. Applicants respectfully submit that the pending claims are in condition for allowance.

I. THE CLAIMS ARE ENABLED UNDER 35 U.S.C. § 112

Acknowledging that claims 43-45 and 56-76 are enabled for methods for treating metastatic melanoma by administration of peptide or antibody antagonists of the ETB receptor, the Examiner contends that the specification does not enable the broader scope of the claims.[1]

A. The treatment of metastatic melanoma by selectively antagonizing the endothelin B receptor (ETB)

In particular, the Examiner contends that claims 43, 56, 60 and 62, which encompass the selective antagonization of the ETB receptor, are broader in scope than the administration of direct antagonists of the ETB receptor which is admittedly enabled by the specification (*p.*2 of the Office Action).

Although the Applicants do not agree with this rejection, in order to expedite prosecution, claims 43, 56, 60, 62 and claims dependent therefrom have been canceled without prejudice to pursuing this subject matter in other applications. Accordingly, the rejection of these claims is rendered moot.

[1] The Applicants take this opportunity to point out that claimed methods are also enabled using known small organic molecule inhibitors of the ETB receptor, discussed in Section II, *infra*.

B. Inhibiting the development of metastatic melanoma in patients having melanoma

In claims 60-76, the Examiner objects to the claim limitation "prevention" of metastases in patients diagnosed with malignant melanoma, as requiring the complete absence of metastases in the individuals. As noted above, claim 60 and claims dependent therefrom have been cancelled; thus, the rejection of claims 60-68 is moot.

Claim 69 has been amended as suggested by the Examiner to recite a "method for inhibiting the development of metastatic melanoma in a patient having melanoma". Thus, the rejection of claims 69-76 under 35 U.S.C. §112, first paragraph has been obviated and should be withdrawn.

II. THE CLAIMS SATISFY THE WRITTEN DESCRIPTION REQUIREMENT UNDER 35 U.S.C. § 112

Claims 43-45, 56-76 are rejected under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner acknowledges that the specification contemplates the use of small organic molecules, peptides, and antibodies that are included within the genus of the selective ETB antagonists claimed. Nevertheless, the Examiner contends that neither the specification nor the prior art identifies specific inhibitors of ETB which are not peptides, and concludes that small organic molecule inhibitors are beyond the scope of the written description. This rejection is in error and should be withdrawn for the reasons detailed below.[2]

At the time the instant specification was filed, numerous examples of non-peptide small molecule selective ETB antagonists were known in the art. As described in the instant specification, the use of such known selective ETB antagonists is encompassed by the methods of the invention (*e.g.*, *p.*16, *ll.* 5-7 and *p.*20, *ll.* 14-18 of the specification). Appendix A attached hereto is a non-exhaustive list of non-peptide small molecule ETB selective antagonists that were known on or before the filing date of the present application. Pharmacodynamic and pharmacokinetic profiles of two small molecule inhibitors of ETB, Ro

[2] The arguments presented herein correspond to those previously made in response to a similar rejection, which was overcome. See, Office Action dated February 25, 2003 (at p.2-3); Arguments presented in response filed July 25, 2003; and withdrawal of rejection (at p.9, paragraph 10 of Office Action dated March 15, 2004).

46-8443 and A-192621, were disclosed by Douglas (1997, *TiPS* 18:408-412 on *p.* 410, column 3, *ll.* 1-14 and Table 4, previously submitted as Reference C07). In addition to Ro 46-8443 and A-192621, the class of known non-peptide small molecule selective inhibitors of ETB includes PD 147452 and PD 151583 (Battistini and Dussault, 1998, *Pulmonary Pharmacology & Therapeutics* 11:97-112 on *p.* 101, column 2, *ll.* 3-10 and Table 1, previously submitted as Reference C03).

Prior to the filing date of the instant specification, the structural features that allow non-peptide small molecules to selectively inhibit ETB over ETA were characterized. Studies were conducted to modulate selective ETA antagonists to produce antagonists that were increasingly specific for ETB (Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316, previously submitted as Reference C04; Mederski et al., 1999, *Bioorganic & Medicinal Chemistry Letters* 9:619-22, previously submitted as Reference C08). Examples of such selective ETB antagonists include Compounds 4c, 4f, 4h-4l, 6b, 6c, 6e, 6f, and Compounds 7aa-7ff (see *p.* 2304, col. 1, *ll.* 29-33; *p.* 2304, col. 2, *ll.* 14-21; and *p.*2306, col. 22, *ll.* 27-33 of Reference C04 and *p.* 622, *ll.* 8-11 of Reference C08, respectively). Not only was one skilled in the art able to identify a selective ETB antagonist, he was also able to modify existing compounds to create a selective ETB antagonist. Thus, one of skill in the art would not only know the structure of the small molecule compounds which could be used in the methods of the invention but also the relationship between that structure and the compound's ability to function as a selective ETB antagonist.

The instant specification teaches methods of using selective ETB antagonists to treat metastatic melanoma. Members of the genus of compounds described for use in the methods of the invention were available at the time of filing and could be readily recognized based on the disclosure by one of skill in the art. The specification need not disclose what one skilled in the art already possesses. Hirschfeld v. Banner, Commissioner of Patents and Trademarks, 200 U.S.P.Q. 276, 281 (D.D.C. 1978), aff'd, 615 F.2d 1368 (D.C. Cir. 1980), cert. denied, 450 U.S. 994 (1981). A patent application need not include in the specification that which is already known to and available to the public. Paperless Accounting Inc. v. Bay Area Rapid Transit System, 804 F.2d 659, 231 U.S.P.Q. 649 (Fed. Cir. 1986), cert. denied , 480 U.S. 933 (1987). The fact that Applicants did not recite these compounds verbatim in the specification should not preclude the specification from meeting the written description requirement. In re Alton, 76 F.3d 1168, 1172, 37 U.S.P.Q.2d 1578, 1581 (Fed. Cir. 1996). Applicants submit

that the claims satisfied the written description requirement and the rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

Claims 60 and 69 have been rejected for lack of support in the originally filed disclosure. Claim 60 has been canceled. Rejection as to this claim is rendered moot. Claim 69 has been amended to recite "a method for inhibiting the development of metastatic melanoma in a patient having a melanoma" as suggested by the Examiner. The rejection is believed to have been overcome.

In view of the foregoing, Applicants request that the Examiner withdraws the rejection under 35 U.S.C. §112, first paragraph.

III. CORRESPONDING EUROPEAN PATENT WITH SIMILAR CLAIMS HAS BEEN GRANTED

Applicants take this opportunity to inform the Examiner that European patent, EP 1 181 555 B1, corresponding to the above-captioned application was granted on December 24, 2008 with similar claims. A copy of the granted European patent is submitted hereiwth, accompanied by a Supplemental Information Disclosure Statement.

Applicants submit that the pending claims in the present application are in condition for allowance.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the rejections in the previous Office Action and a notice of allowance are earnestly requested. Applicants respectfully submit that the pending claims are in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: February 17, 2009

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APPENDIX A

ETB selective antagonist	Class of Inhibitor	Reference
Ro 46-8443	non-peptide small molecule	Breu et al., 1996, *FEBS Lett.* 383:37-41 and Douglas, 1997, *TiPS* 18:408-412
A-192621	non-peptide small molecule	Douglas, 1997, *TiPS* 18:408-412 and Battistini and Dussault, 1998, *Pulmonary Pharmacology & Therapeutics* 11:97-112
PD 147452	non-peptide small molecule	Battistini and Dussault, 1998, *Pulmonary Pharmacology & Therapeutics* 11:97-112
PD 151583	non-peptide small molecule	Battistini and Dussault, 1998, *Pulmonary Pharmacology & Therapeutics* 11:97-112
Compound 4c	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 4f	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 4h	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 4i	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 4j	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 4k	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 4l	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 6b	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 6c	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 6e	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 6f	non-peptide small molecule	Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316
Compound 7aa	non-peptide small molecule	Mederski et al., 1999, *Bioorganic & Medicinal Chemistry Letters* 9:619-22

Compound 7bb	non-peptide small molecule	Mederski et al., 1999, *Bioorganic & Medicinal Chemistry Letters* 9:619-22
Compound 7cc	non-peptide small molecule	Mederski et al., 1999, *Bioorganic & Medicinal Chemistry Letters* 9:619-22
Compound 7dd	non-peptide small molecule	Mederski et al., 1999, *Bioorganic & Medicinal Chemistry Letters* 9:619-22
Compound 7ee	non-peptide small molecule	Mederski et al., 1999, *Bioorganic & Medicinal Chemistry Letters* 9:619-22
Compound 7ff	non-peptide small molecule	Mederski et al., 1999, *Bioorganic & Medicinal Chemistry Letters* 9:619-22